Editorials

On Violating Promises

SOME MONTHS AGO *American Medical News* reprinted an article by Harry Schwartz that had been published by *The New York Times*. It pointed out that, of all Americans, doctors who treat Medicare patients are the only ones legally compelled not to raise their fees. It was his opinion that doctors are getting a raw deal, and surely there is support for this opinion among physicians. He went on to point out that the mandated freeze on these physicians' fees violated "openly and plainly" the promise made to physicians when the Medicare law was passed in 1966, and speculated on what might happen if government promises made to other citizens were also to be violated. He notes that "when government openly and enthusiastically violates its promises to one important group of Americans—doctors—the precedent has been set for violating promises to others" and asks "if breaking promises to doctors is all right, then what's wrong with breaking promises to 'rich' people who own government securities," for example.

These are times when what happens in health care may be a bellwether for what could happen elsewhere in our society. As Schwartz points out, government has made many promises to many people over the years, and when these are not kept, for whatever reason, trust in government and therefore in the American system becomes eroded, with eventual economic and political consequences no one really wants to think about. Schwartz's point could prove to be an important one, or so it seems to this writer.

MSMW

Navigating the Sea of Eicosanoids

"PROSTAGLANDINS, THROMBOXANES AND LEUKOTRIENES in Clinical Medicine" by Zipser and Laffi introduces the fundamental concepts critical to an understanding of the structural diversity and functional complexity of eicosanoid metabolites of arachidonic acid. Many of the metabolites generated by the enzymatic actions of cyclooxygenases and lipoxygenases on arachidonic acid are potent mediators of cellular and organ system responses that have potentially important roles in physiologic processes and disease states. The combined effects of multiple eicosanoid mediators that differ in action and potency often determine the overall biological response. A further element of adaptability is provided by the varied mechanisms of recognition and regulation of the mediators by target cells.

Generation and biodegradation of some products of the oxygenation of arachidonic acid involve one or more cell-cell interactions. For example, some 15-lipoxygenase products from eosinophils, epithelial cells and endothelial cells stimulate 5-lipoxygenase activity in mast cells and inhibit that expressed in macrophages and neutrophils.[1,2] The 5-hydroxy-eicosatetraenoic acid (5-HETE) released by neutrophils, macrophages or mast cells may be converted to double oxygenation products by 15-lipoxygenases of eosinophils or 12-lipoxygenases of platelets in mixed cell populations.[3] Cellular cooperativity not only leads to the production of novel dihydroxy and trihydroxy eicosanoid mediators with distinct activities, but also enhances the generation of mediators by any one type of cell through stimulatory factors released by another cell. In addition, some cells appear to degrade eicosanoid mediators released by other cells engaged in active synthesis. C-6 peptide leukotrienes synthesized by macrophages or mast cells are inactivated by halide-dependent peroxidases released from eosinophils.[4] Knowledge of these concerted synthetic mechanisms and pathways of degradation is critical to the interpretation of data from in vitro studies of isolated cells in relation to their significance in vivo.

A separate set of stereospecific receptors on target cells transduces the effect of each eicosanoid mediator.[5-7] Some target cells express subsets of receptors for a single mediator that transduce different functional responses. For example, human neutrophils have a high-affinity subset of receptors for leukotriene (LT) B_4 that are coupled to activation of chemotaxis and increased adherence and a low-affinity subset that elicits release of lysosomal enzymes and enhanced oxidative metabolism.[8] Thus, two concentrations of an eicosanoid mediator may interact with even one type of cell through different receptors with qualitatively distinct consequences. The choice of a pharmacologic antagonist may require estimation of the expected concentrations of such mediators for optimally specific competition at the receptor level.

The presence of different eicosanoid receptors that transduce specific effects suggests the possibility of finding biologically opposite effects of two eicosanoid mediators generated by the same pathway in one tissue. Thromboxane (Tx) A_2 and prostaglandin (PG) I_2 are generated when platelets adhere to damaged vascular endothelium. TxA_2 stimulates vasoconstriction and platelet aggregation, whereas PGI_2 promotes vasodilation and inhibits platelet aggregation. Thus it may be difficult to predict the results of inhibition of the shared pathway that produces TxA_2 and PGI_2 unless differences exist in the susceptibility to inhibition of activity of later synthetic steps. Opposite actions of a single mediator are sometimes identified in different types of target cells. For instance, LTB_4 stimulates the functions of T-suppressor cells and inhibits those of T-helper cells in vitro.[9] In other organ systems, the effects of eicosanoid mediators are additive or synergistic.

Some eicosanoid mediators act as second messengers for the primary actions of other eicosanoids. LTB_4 acts principally to augment the leukocytic components of inflammation. It also evokes bronchospasm, although with far lower potency than LTC_4 or LTD_4. The mechanism of transduction of the weaker effects of LTB_4 involves stimulation of the cyclooxygenation of arachidonic acid by target tissues, which leads to local generation of the potent bronchoconstrictor TxA_2. Inhibitors of cyclooxygenation thus may suppress the effects of 5-lipoxygenase-derived mediators.[10-12] In some instances, eicosanoids may condition the responses of tissues to other

eicosanoids and other mediators. LTE_4 alone stimulates bronchoconstriction. However, at concentrations below the threshold for a direct response, LTE_4 enhances bronchial reactivity to other bronchoconstrictors such as histamine.[13] Similarly, intradermally administered LTB_4 has the capacity to induce hyperalgesia, which augments the perception of subsequently applied noxious stimuli.[14]

The duration of exposure of a target tissue to any concentration of an eicosanoid mediator may modify the nature and magnitude of the response. Neutrophils preincubated with LTB_4 will later be less chemotactically responsive to this mediator due to a down-regulation of the number of high-affinity receptors.[8] Effects such as these may be relevant in disease processes such as adult respiratory distress syndrome, where pulmonary edema fluid contains greatly increased levels of LTD_4 and LTE_4 for many hours.[15] In spite of this, these patients do not show evidence of bronchospasm. This suggests that the airway smooth muscle is in a selectively refractory state, while the endothelial-epithelial cell network responds appropriately to the LTD_4 and LTE_4 with altered permeability and fluid transudation.

The principal task that must precede major pharmacologic manipulation of arachidonic acid metabolism in many complex diseases is the determination of relevance of elevated concentrations of potent eicosanoid mediators in tissue fluids. Chromatographic and immunochemical techniques of measurement and identification of the mediators are now available for sensitive and accurate assessment in disease states. In most diseases where tissue concentrations of the mediators are elevated, it is not known if they are primary pathogenic factors, secondary accessory elements or irrelevant reflections of the underlying condition. The results of carefully defined studies in vitro and in animals may help to resolve these issues.

Drugs can be developed that will affect the generation, activity and metabolism of eicosanoid mediators. The current dilemma and the opportunity, which are inextricably intertwined, are that drugs must be developed as pharmacologic probes in order to establish any involvement of the mediators in pathogenesis. Although the results of such studies may relegate the drugs to obsolescence immediately, the wide tissue distribution and the protean effects of these mediators favor the inevitable establishment of multiple physiologic and pathologic roles for the eicosanoids.

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Caring for the Poor

THERE IS an aspect of competition, whether in business or health care, that has been receiving relatively little attention of late. Those who lose out in the competition are left pretty much to fend for themselves. It is one thing if they are healthy, physically and mentally able to compete again, but another if they are not. Through most of history the sick, ailing or unfit have received short shrift, sometimes even at the hands of the medical profession. Darwin's law prevailed. The fit tended to survive and to succeed while the unfit did not. But modern medicine and modern social philosophy began to change all this, at least in western nations. Modern medicine made it possible to do more for the sick and unfit, and the new social policies tried to make the new health care available to all who needed it. The pendulum swung toward a more egalitarian approach, whether toward women, minorities, the disadvantaged or the unfit. Then, particularly in health care, the costs rose, and in the name of competition (to help reduce costs) the profit motive was blessed for the delivery of health care. But predictably, it is not proving profitable to provide health care for people who cannot pay for it. Both the private sector and government are now backing off from adequately financing health care for the poor, and there is now beginning to be evidence that at least some of the poor are not getting all the care they need, at least as soon as they need it.

So far this has not surfaced as a very large problem. Perhaps much of the health care now being rendered is not really necessary. Perhaps the poor or the unfit are not organized enough to protest the short shrift they are apparently receiving. Maybe we are moving de facto toward identifying an acceptable basic, frill-free or "generic" health care that will prove adequate enough though much less costly. In any case, there are not yet any inescapably persuasive data that indicate the health of the poor or unfit to be significantly worse as a result of their being victims of the competitive approach to financing health care in this nation. But the competitive process has not yet run its full course, and government has not yet cut back on financing health care for the poor and unfit as far as it no doubt will. But it would seem predictable that at some point things will get bad enough so that the conscience of America will be pricked again and, once more, something will be done about health care for the poor.